5-alpha reductase deficiency

5-alpha reductase deficiency is a condition that affects male sexual development before birth and during puberty. People with this condition are genetically male, with one X and one Y chromosome in each cell, and they have male gonads (testes). Their bodies, however, do not produce enough of a hormone called dihydrotestosterone (DHT). DHT has a critical role in male sexual development, and a shortage of this hormone disrupts the formation of the external sex organs before birth.

Many people with 5-alpha reductase deficiency are born with external genitalia that appear female. In other cases, the external genitalia do not look clearly male or clearly female (sometimes called ambiguous genitalia). Still other affected infants have genitalia that appear predominantly male, often with an unusually small penis (micropenis) and the urethra opening on the underside of the penis (hypospadias).

During puberty, people with this condition develop some secondary sex characteristics, such as increased muscle mass, deepening of the voice, development of pubic hair, and a growth spurt. The penis and scrotum (the sac of skin that holds the testes) grow larger. Unlike many men, people with 5-alpha reductase deficiency do not develop much facial or body hair. Most affected males are unable to father a child (infertile).

Children with 5-alpha reductase deficiency are often raised as girls. About half of these individuals adopt a male gender role in adolescence or early adulthood.

Frequency

5-alpha reductase deficiency is a rare condition; the exact incidence is unknown. Large families with affected members have been found in several countries, including the Dominican Republic, Papua New Guinea, Turkey, and Egypt.

Genetic Changes

Mutations in the *SRD5A2* gene cause 5-alpha reductase deficiency. The *SRD5A2* gene provides instructions for making an enzyme called steroid 5-alpha reductase 2. This enzyme is involved in processing androgens, which are hormones that direct male sexual development. Specifically, the enzyme is responsible for a chemical reaction that converts the hormone testosterone to DHT. DHT is essential for the normal development of male sex characteristics before birth, particularly the formation of the external genitalia.

Mutations in the *SRD5A2* gene prevent steroid 5-alpha reductase 2 from effectively converting testosterone to DHT in the developing reproductive tissues. These hormonal

factors underlie the changes in sexual development seen in infants with 5-alpha reductase deficiency.

During puberty, the testes produce more testosterone. Researchers believe that people with 5-alpha reductase deficiency develop secondary male sex characteristics in response to higher levels of this hormone. Some affected people also retain a small amount of 5-alpha reductase 2 activity, which may produce DHT and contribute to the development of secondary sex characteristics during puberty.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the *SRD5A2* gene in each cell have mutations. Most often, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition.

Although people who are genetically female (with two X chromosomes in each cell) may inherit mutations in both copies of the *SRD5A2* gene, their sexual development is not affected. The development of female sex characteristics does not require DHT, so a lack of steroid 5-alpha reductase 2 activity does not cause physical changes in these individuals. Only people who have mutations in both copies of the *SRD5A2* gene and are genetically male (with one X and one Y chromosome in each cell) have the characteristic signs of 5-alpha reductase deficiency.

Other Names for This Condition

- Familial incomplete male pseudohermaphroditism, type 2
- male pseudohermaphroditism due to 5-alpha-reductase deficiency
- PPSH
- Pseudovaginal perineoscrotal hypospadias
- Steroid 5-alpha-reductase deficiency

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: 3-Oxo-5 alpha-steroid delta 4-dehydrogenase deficiency https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268297/

Other Diagnosis and Management Resources

- MedlinePlus Encyclopedia: Ambiguous Genitalia https://medlineplus.gov/ency/article/003269.htm
- MedlinePlus Encyclopedia: Intersex https://medlineplus.gov/ency/article/001669.htm

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Ambiguous Genitalia
  https://medlineplus.gov/ency/article/003269.htm
- Encyclopedia: Intersex
  https://medlineplus.gov/ency/article/001669.htm
- Health Topic: Endocrine Diseases
  https://medlineplus.gov/endocrinediseases.html

Genetic and Rare Diseases Information Center

- 5-alpha reductase deficiency
  https://rarediseases.info.nih.gov/diseases/5680/5-alpha-reductase-deficiency

Educational Resources

- American Psychologial Association: Answers to Your Questions About Individuals With Intersex Conditions
  http://www.apa.org/topics/lgbt/intersex.pdf
- Disease InfoSearch: Pseudovaginal perineoscrotal hypospadias
  http://www.diseaseinfosearch.org/Pseudovaginal+perineoscrotal+hypospadias/6052
- MalaCards: 5-alpha reductase deficiency
  http://www.malacards.org/card/5_alpha_reductase_deficiency

- My46 Trait Profile
  https://www.my46.org/trait-document?trait=5-alpha%20reductase%20deficiency&type=profile
- Orphanet: 46,XY disorder of sex development due to 5-alpha-reductase 2 deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=753

Patient Support and Advocacy Resources

- Accord Alliance
  http://www.accordalliance.org/
- Resolve: The National Infertility Association
  http://www.resolve.org/
- Resource list from the University of Kansas Medical Center: Ambiguous genitalia
  http://www.kumc.edu/gec/support/ambig.html

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%285-alpha+reductase+deficiency%5BTIAB%5D%29+OR+%28ppsh%5BTIAB%5D%29+OR+%28pseudovaginal+perineoscrotal+hypospadias%5BTIAB%5D%29+OR+%28steroid+5-alpha-reductase+deficiency%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- PSEUDOVAGINAL PERINEOSCROTAL HYPOSPADIAS
  http://omim.org/entry/264600

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